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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
BARNHART, LORA ELIZABETH	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,086	QUESENBERRY, PETER J.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11-30,32-41,54-62 and 64-81* is/are pending in the application.

4a) Of the above claim(s) *14-28 and 32-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,11-13,29,30,54-62 and 64-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 4/20/10 to claims 1, 3, 4, 6-9, 11-13, 29, 30, 54, and 56-62 have been entered. Claims 5, 10, 31, and 63 have been canceled. Claims 65-81 have been added. Claims 1-4, 6-9, 11-30, 32-41, 54-62, and 64-81 remain pending in the current application, of which claims 1-4, 6-9, 11-13, 29, 30, 54-62, and 64-81 are being considered on their merits. Claims 14-28 and 32-41 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Drawings

The examiner indicated in the 10/20/09 Office action that the drawings submitted 12/23/05 were acceptable; however, closer scrutiny of the application file revealed a discrepancy that must be rectified. Applicant actually submitted two different sets of drawings on 12/23/05. One set appears to be identical to that submitted in the parent PCT application; the other appears to have made cosmetic changes such as placing the text in all caps. However, it is not clear which set is the original and which is the amended set. There can be only one original submission of drawings. Applicant is requested to re-submit the drawings, indicating that they are replacement sheets; applicant is also requested to indicate any differences between the two 12/23/05 submissions that are NOT merely cosmetic.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-9, 11-13, 29, 30, 54-62, and 64-81 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1 and 54 comprise three steps: (a) culturing purified bone marrow stem cells (BMSCs) from resting state under synchronizing conditions; (b)

contacting the BMSCs of step (a) with a growth factor; and (c) subculturing the cells of (b) until differentiated hematopoietic cells are produced. The claims as amended are confusing because each step does not have a clear relationship to the one preceding it. For example, step (b) as amended in each claim refers to "the cells of step (a)," which could reasonably refer to the purified BMSCs or to the BMSCs after they have been synchronized. The issue is further clouded by the fact that in applicants' working examples, the "conditions that promote synchronous progression through the cell cycle" include incubation with growth factors and cytokines. See page 6, lines 28-31; page 10, lines 16-18; and Figure 1. It is not clear whether the "contacting with growth factors" of step (b) is the same as the "synchronizing" of step (a), since both employ growth factors and/or cytokines. Clarification is required.

Claim 68 refers in step (b) to "the synchronous cells of step (a)," but there is no antecedent basis for this limitation in step (a). Step (a) does not recite "the synchronous cells." Furthermore, step (a) only requires that synchronous progression through the cell cycle be "promoted," not that it actually occurs. Step (a) does not necessarily yield "synchronous cells." Clarification is required.

Claims 74 and 78 both include extensive functional language in step (b), i.e. the limitations beginning with "wherein." The examiner has discussed functional language previously. See page 7 of the 10/20/09 Office action. In brief, "[w]hen a claim limitation is defined in purely functional terms, the task of determining whether that limitation is sufficiently definite is a difficult one that is highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the

relevant art area). We note that the patent drafter is in the best position to resolve the ambiguity in the patent claims, and it is highly desirable that patent examiners demand that applicants do so in appropriate circumstances so that the patent can be amended during prosecution rather than attempting to resolve the ambiguity in litigation." *Halliburton Energy Services, Inc. v. M-I LLC*, 85 USPQ2d 1654, 1663 (Fed. Cir. 2008). While functional claiming is authorized by 35 U.S.C. § 112, sixth paragraph, that statute was enacted specifically to preclude overly broad claims that effectively purport to cover any and all limitations, so long as they perform the required functions. Specifically, claims that are ambiguous as to boundaries for functional limitations may be indefinite and do not distinguish the claimed product over the prior art. Here, step (b) in both claims 74 and 78 is indefinite in that it requires a "specific" phase of the cell cycle without providing criteria for the selection of that phase other than the circular requirement that it "promote" a "specific" differentiation pathway. The claim defines the time point in step (b) wholly in terms of some undefined outcome that may or may not come to pass (as discussed above, "promote" is not synonymous with "yield"). Step (b) makes an effort to define the method solely in terms of its outcome, which is indefinite because the metes and bounds of the steps are not clearly defined. It is not clear which steps are included and which are excluded. Clarification is required.

Because claims 2-4, 6-9, 11-13, 29, 30, 55-62, 64-67, 69-73, and 75-81 depend variously from indefinite claims 1, 54, 68, 74, and 78 and do not clarify the points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

The term "differentiation hotspot" in claims 29, 61, 70, 76, and 80 is not adequately defined in the specification, nor is it a term of art. At page 5, lines 23-28, the specification indicates that "differentiation hotspots" are "points where a specific differentiation pathway is favored," but it is not clear from this definition whether the hotspot is a set point in the cell cycle or whether it varies for each pathway and in what manner. Clarification is required. Applicant has not addressed this issue by amendment or particular comment. The rejection stands and is extended to the new claims that recite the limitation. The examiner queries whether these claims effectively further limit their independent claims, since they appear to be merely giving a name to a phenomenon that occurs during the claimed method. If the latter is the case, the examiner submits that canceling these claims would not impact the scope of the claimed subject matter and would simplify the matters at issue.

Claims 30, 62, 71, 77, and 81 require that the predetermined phase comprise a "reversible differentiation hotspot," which is confusing because it is not clear whether the hotspot is reversible (i.e., sometimes it is a hotspot, sometimes it is not) or whether the differentiation itself is reversible. Furthermore, it is not clear how the limitations "a differentiated cell" and "a stem cell" relate to the cells recited in claim 1. Clarification is required. Applicants are "perplexed" by this rejection, citing a portion of the specification and referring generally to the Quesenberry declaration, but the examiner submits that the language in the claims does not appear in the cited passage and that the claim language still has two equally reasonable interpretations (reversible hotspot vs. reversible differentiation). The cited claims make no mention of "cellular de-

differentiation," so applicant's comments are not germane to the claims. Applicant must clarify this matter within the claim language to overcome this rejection. However, as discussed above for claims 28, 61, 70, 76, and 80, claims 30, 62, 71, 77, and 81 appear to be merely giving a name to a phenomenon that occurs during the claimed method. If the latter is the case, the examiner submits that canceling these claims would not impact the scope of the claimed subject matter and would simplify the matters at issue.

Claims 64, 65, and 72 depend from claims 54, 1, and 68, respectively, and refer to "the bone marrow stem cells" of each independent claim. This is confusing because each of the independent claims refers to several different versions of BMSCs: the purified BMSCs at resting state, the BMSCs in which synchronous progression through the cell cycle has been promoted, and the BMSCs contacted with growth factors. It is not clear to which of these population claims 64, 65, and 72 refer. Furthermore, it is not clear whether the cells of claims 64, 65, and 72 are those that are contacted and "subcultured," particularly in view of the limitation s of claims 66, 67, and 73, which require sorting the cells before carrying out step (a) but are silent as to any link between the sorting step and the properties in claims 64, 65, and 72. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-9, 11-13, 29, 30, 54-62, 64, 65, 68-72, and 74-81 are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Hagihara et al. (2001, *Journal of Immunological Methods* 253: 45-55; on 2/27/06 IDS). The amendments to the claims necessitate this rejection.

Hagihara teaches a method for the production of differentiated hematopoietic cells including dendritic cells. See abstract. Hagihara's method comprises purifying CD34+ stem cells from bone marrow (BMSCs) to 94-96% purity by density gradient centrifugation. See section 2.2 at page 47 and Table 1 at page 48. Hagihara teaches culturing their purified CD34+ (BMSCs) in a medium comprising steel factor, thrombopoietin, and FLT-3 ligand for weeks; then contacting the cells with growth factor GM-CSF; then subculturing the cells with GM-CSF for 14 days. See section 2.4 at page 49.

M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application. In this case, even if applicant had identified some previously unappreciated properties of Hagihara's method steps (which the examiner does not concede), the steps themselves would not become patentable. See *Titanium Metals Corp. v. Banner,* 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Hagihara teaches steps that overlap with the instantly claimed steps, and the examiner notes that Hagihara's cocktail (Flt-3, SCF, and TPO) is identical to that employed by applicants in the working examples. See specification, page 10, line 16, e.g.; the molecule called

"steel factor" is also known as "stem cell factor" or SCF (see Toksoz et al., 1992, *Proceedings of the National Academy of Sciences USA* 89: 7350-7354; attached as reference U). The examiner also notes that this combination of factors was known in the art at the time of filing to synchronize the cell cycle of cultured BMSCs. See Colvin et al., 2002, *In Vitro Cellular and Developmental Biology -- Animal* 38:343-351, at Figure 7; attached as reference V; see also Feng Yan et al., already of record.

Claims 4, 54, 57, and 59 do not clearly limit the claims, because they appear merely to recite properties of the cell cycle of synchronized BMSCs.

Regarding claims 13, 60, 69, 75, and 79, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step. The fact that Hagihara may not have recognized that their steps also yielded the cell types recited in claims 7-9, 12, and 54 is immaterial, since steps necessarily yield all of their inherent effects, whether the experimenter appreciates them or not. Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) at 780. If applicants' method differs materially from Hagihara's, e.g. by amounts of growth factors or timing of culture steps, the claims should so recite.

As discussed above in the indefiniteness rejections, claims 29, 30, 61, 62, 70, 71, 76, 77, 80, and 81 appear merely to give a name to a phenomenon that occurs during the positively recited culturing steps of the claims, so they do not clearly limit the claims. Applicants' disclosure appears to be an investigation of a mechanism in which particular

points in the cell cycle are more conducive to yielding one endpoint over another. However, [p]atents are not awarded for academic theories, no matter how groundbreaking or necessary to the later patentable inventions of others." *Ariad Pharms. Co. v. Eli Lilly & Co.*, 94 U.S.P.Q.2d 1161, 1173 (Fed. Cir. 2010) (en banc). The patent system is designed to give incentives to complete inventions, not to guess at the future. *Id.* at 1174. Methods are defined by their steps, not by any underlying mechanism. The fact that Hagihara did not recognize the presence of a "hotspot" within their culturing steps cannot distinguish that reference from the claimed method as long as the positively recited steps are taught by the reference.

As discussed above, the amendments to claims 1, 54, and 68 introduce uncertainty into the limitations of claims 65, 64, and 72, which depend from them and refer to some population of BMSCs within those claims. Claims 64, 65, and 72 do not clearly limit the independent claims.

Regarding the art rejections of record, applicant alleges that Hagihara does not teach contacting the cells at any particular phase of the cell cycle. See reply, pages 23-24. Applicant alleges that the examiner has misinterpreted the claims. See reply, page 24. Regarding the Quesenberry declaration, which was submitted with the 8/11/09 reply, applicant refers to a 2010 publication by Colvin et al. and alleges that "data confirming cell differentiation relative to cell cycle" has been published. See reply, page 25.

As discussed above, the claims do not require that the contacting commence at any particular point in the cell cycle, only that cells be contacted at a particular point. A

method like Hagihara's, which teaches continuous contact over 14 days, includes contact 32 and 40 hours from the start of culturing.

The use of the transitional phrase "comprising" applicant advocates is completely inconsistent with accepted PTO practice. M.P.E.P. § 2111.03 explicitly directs that this term is "inclusive or open-ended and does not exclude additional, unrecited elements or method steps." See, *e.g.*, *Invitrogen Corp. v. Biocrest Mfg.*, L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003). There is no basis for applicant's urging at page 24 that a method "comprising" steps (a), (b), and (c) contains those steps and no others. The instant claims might fairly encompass, e.g., a method containing a step in which additional cells are added to the culture of step (a). None of the claims requires that the cells of step (a) are the only cells within the culture. Coculturing undifferentiated cells on feeder cell layers (which are, in effect, living "growth factors") is, in fact, standard practice in the art (see, e.g., Namen et al., 1990, U.S. Patent 4,965,195, at column 2, lines 19-26; reference B), so constraining the claims as applicant advocates would be improper. It is not clear how adding other cells would be "contrary to the limitations of step (a) and step (b)."

Regarding the Colvin 2010 reference, the examiner has considered the portions to which applicant directs attention, but like the Quesenberry declaration, these figures and tables do not clearly share a nexus with the claims. Figure 3 appears to represent an experiment in which BMSCs are cultured for particular set amounts of time (including 32 and 40 hours) in a combination of SCF/SF, Flt-3, and TPO and then "stimulated" with G-CSF, GM-CSF, and SF/SCF for some unspecified time. The methods in the current

independent claims require synchronizing cells under certain "conditions," then contacting them with a "growth factor or cytokine" at a particular point in their cell cycle, then culturing them until differentiated hematopoietic cells are produced. Tables 2 and 3 and Figures 5-7 have also been noted, but none of these addresses the claims across their breadth, and none is persuasive that the steps of Hagihara's method are distinct from the instant steps.

The Quesenberry declaration argues that Hagihara teaches culturing for particular times, while the instant method is "directed to a specific phase of the cell cycle, . . . regardless of when in that time that phase occurs." See page 8, near the center of the page. The examiner queries the difference as far as it is relevant to the properties of the positively recited method steps, since Figure 3 of Colvin 2010 clearly teaches culturing BMSCs in SCF/SF, Flt-3, and TPO for various times.

The examiner further notes that none of the methods requires that any particular type of differentiated hematopoietic cells be produced in any particular amount or to the exclusion of any other type. For example, claim 7 requires that the product of claim 1 yield "a plurality [i.e., at least two] of megakaryocytes." There is no requirement in claim 54 that when, for example, megakaryocytes are produced, mature granulocytes are not. All that claim 54 requires is that the product "comprise" particular cell types. See M.P.E.P. § 2111.03. Applicant's instant remarks and those of record urge that there is some relationship between the selection of a particular cell cycle phase and the production of a particular cell type and no others. The claims, however, do not make such a stringent requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 11, 13, 29, 30, 65, 68-72, and 74-81 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara et al. (2001, *Journal of Immunological Methods* 253: 45-55) taken with Feng Yan et al. (2000, *Blood* 96: 680a) and Messner et al. (1987, *Blood* 70: 1425-1432).

Hagihara teaches a method for the production of differentiated hematopoietic cells including dendritic cells. See abstract. Hagihara's method comprises purifying CD34+ stem cells from bone marrow (BMSCs) to 94-96% purity by density gradient centrifugation. See section 2.2 at page 47 and Table 1 at page 48. Hagihara teaches culturing their purified CD34+ (BMSCs) in a medium comprising steel factor, thrombopoietin, and FLT-3 ligand for weeks; then contacting the cells with growth factor GM-CSF; then subculturing the cells with GM-CSF for 14 days. See section 2.4 at page 49. Hagihara does not indicate that the growth factor must be added for the first time during any particular cell cycle phase (although, as discussed above, the claims also make no such requirement; see M.P.E.P. § 2111.03).

Yan teaches that the combination of factors SCF, TPO and FLT-3 in the culture medium stimulates the hematopoietic bone marrow cells to enter into synchronous cell cycle from resting state. For example, see the abstract of Yan, which clearly discloses

that the purified bone marrow cells were quiescent (non-diving or "resting" at G0/G1 phase) at the beginning of the culture, that the addition of cytokines SCF, TPO and FLT-3 stimulated the cells to enter into the cycle, and that the amount of synchronous cells in S phase increased during culturing in the presence of cytokines SCF, TPO and FLT-3.

Messner teaches that cell cycle studies and stem cell engraftment studies indicate that the higher than normal proportions of multipotential hematopoietic cells are present in S phase during progression of the hematopoietic cells through the cell cycles. See abstract, e.g.

Regarding claim 13, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step.

As discussed above, claims 29, 30, 70, 71, 76, 77, 80, and 81 do not clearly limit the independent claims, in part because they appear solely to describe inherent properties of the steps. Claims 4 and 11 do not clearly limit the claims, because they appear merely to recite properties of the cell cycle of synchronized BMSCs. As discussed above, the amendments to claims 1 and 68 introduce uncertainty into the limitations of claims 65 and 64, which depend from them and refer to some population of BMSCs within those claims. Claims 64 and 65 do not clearly limit the independent claims.

A person of ordinary skill in the art would have had a reasonable expectation of success in synchronizing the BMSCs of Hagihara using Hagihara's medium containing SCF, TPO, and FLT-3 ligand because Yan teaches that such a medium promotes

synchronous progression through the cell cycle. The skilled artisan would have been motivated to synchronize the cells in order to obtain more consistent results from the culturing step, especially given Messner's teaching that the cell cycle phase affects the proportion of multipotential cells in a population.

The skilled artisan would have had a further reasonable expectation of success in synchronizing the cells and adding growth factor or cytokine (in this case, the GM-CSF of Hagihara) at various phases of the cell cycle because Messner teaches that more hematopoietic stem cells are at S phase than other cell cycle phases. The skilled artisan would have been motivated to determine the differentiability of Hagihara's stem cells at various points in the cell cycle in order to maximize the number of stem cells available for Hagihara's differentiation protocol. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (U.S. 2007). In this case, there are only a few different points in the cell cycle, and Messner teaches that these points were well known at the time of the invention; testing stem cells at each of these points to identify their propensity for differentiation would have constituted routine experimentation at the time of the invention.

It would therefore have been obvious to a person of ordinary skill in the art at the

time the invention was made to synchronize the cells of Hagihara with the medium of Hagihara and Yan and then to treat the synchronized cells at various points within the cell cycle in order to determine the optimal conditions for Hagihara's differentiation method.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Regarding the pertinent rejection of record, applicant alleges that the skilled artisan would have assumed that BMSCs would be homogeneous and clonal in nature, referring generally to the Quesenberry declaration. See reply, page 27. Applicant alleges that Messner investigated the cell cycle of bone marrow for a different reason than that considered relevant in the instant claims. See reply, pages 27-28. These arguments have been fully considered, but they are not persuasive.

There is no evidentiary basis for the Quesenberry declaration's characterization of the prevailing assumptions in the art about BMSCs. As discussed previously, that declaration contains only the opinion of the inventor himself, and evidence is necessary to overcome the examiner's *prima facie* obviousness rejection, which was based on art teachings. Applicant refers to an unidentified portion of the Quesenberry declaration that presumably alleges that the skilled artisan would have presumed that a population of BMSCs would be "homogeneous and clonal in nature," but the Colvin 2010 publication, which applicant submitted with the instant reply to supplement the Quesenberry declaration, characterizes CFU-S, which are immature hematopoietic stem cells derived from bone marrow, as "heterogeneous." See page 57, column 1.

The Colvin 2010 publication refers to a 1964 study that concluded that CFU-S are heterogeneous and unpredictable, and it further discusses studies from as early as 1987 tending to show that CFU-S are heterogeneous. See *id.* Regarding the LRH cells of the Quesenberry declaration and the instant specification, Colvin 2010 refers to 1 1991 publication and indicates that "[o]ne in 3-4 of these cells will form high-proliferative potential (HPP) colonies," which suggests that the art never considered LRH cells to be "homogeneous and clonal in nature." The examiner queries this seeming inconsistency.

In response to applicant's argument that Messner was concerned with a different aspect of BMSC cell cycling, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Yan teaches that synchronizing BMSCs was known in the art, and Messner's teachings suggest that the multipotentiality of BMSCs varies during the cell cycle. When Hagihara's teaching of culturing BMSCs first in a cocktail that Yan teaches synchronizes cells, then in a differentiation-inducing culture media, is considered with Messner's suggestion that cell cycle affects multipotentiality, the invention becomes obvious. The examiner emphasizes again for the record that the claims do not require adding growth factors at any particular time, only that BMSCs be in contact with the factors at a given point.

Claims 7-9, 54-62, and 64 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara, Yan, and Messner as applied to claims 1-6, 11, 13, 29, 30,

65, 68-72, and 74-81 above, and further in view of Klabusay et al. (2002, *Blood* 100: Abstract No. 4118) and Ramsfjell et al. (1996, *Blood* 88: 4481-4492).

The teachings of Hagihara are relied upon as above. Regarding claim 60, Hagihara's method includes separating the cells induced to become dendritic cells from those BMSCs that carry on the culture; this separating is reasonably considered an "isolating" step.

As discussed above, claims 61 and 62 do not clearly limit the independent claims, in part because they appear solely to describe inherent properties of the steps. As discussed above, the amendments to claim 54 introduces uncertainty into the limitations of claim 64, which depends from it and refers to some population of BMSCs within those claims. Claim 64 does not clearly limit its independent claim.

Hagihara does not teach culturing in G-CSF. Hagihara does not teach all of the end points in claims 7-9, 12, and 54. Hagihara does not discuss the markers in claims 64, 65, and 72.

Klabusay teaches that hematopoietic stem cells are able to regenerate hematopoiesis in all lineages and that addition of G-CSF to their medium will significantly increase the number of maturated cells including granulocytes. See abstract, e.g.

Ramsfjell teaches that culturing stem cells in SCF enhances megakaryocyte differentiation, as well as production of granulocytes and other mature hematopoietic cell types. See abstract, e.g. Ramsfjell teaches that when megakaryocytes mature, they produce platelets. *Id.*

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the G-CSF of Klabusay or the SCF of Ramsfjell for the GM-CSF of Hagihara in Hagihara's method taken in view of Yan and Messner because Klabusay and Ramsfjell teach that G-CSF and SCF affect the differentiation of Hagihara's cells. The skilled artisan would have been motivated to make such a substitution to determine whether Hagihara's method can be used with Klabusay's and Ramsfjell's growth factors/cytokines to direct differentiation to the endpoints already associated by Klabusay and Ramsfjell with those growth factors/cytokines. Varying Hagihara's method using these two different growth factors/cytokines and assaying for directed differentiation to the limited outcomes taught by Klabusay and Ramsfjell would have constituted routine experimentation at the time of the invention. See *KSR* at 1397.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to vary the growth factor/cytokine in Hagihara's differentiation method in order to identify the effects of such variance on that method because Klabusay and Ramsfjell identified links between various growth factors and particular differentiation endpoints.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Regarding the pertinent rejection of record, applicant relies on arguments made against the above rejections, and those arguments are unpersuasive for the reasons given above. See reply, page 30. Applicant alleges that the instant invention "goes far beyond a combination, simple substitution, or improvement of known elements or

methods." See reply, pages 30-31. These arguments have been fully considered, but they are not persuasive. This rejection is, in fact, a substitution of one set of growth factors (Klabusay's G-CSF or Ramsfjell's SCF) for another (Hagihara's GM-CSF). As set forth above and in the references, it was known at the time of the invention that each of these growth factors affects the differentiation pathways hematopoietic cells follow *in vitro*, and the art also correlated each with a particular endpoint (e.g., G-CSF promotes granulocyte maturation). They therefore constitute a finite number of identified, predictable solutions to the same problem, namely the differentiation of BMSCs into various hematopoietic cell types. It is not clear which element of the claimed methods is unpredictable; applicant's attention is drawn to the examiner's above discussions of the scope of the instant claims.

Applicants' statements that the prior art's methods are unpredictable are further queried, given the specification's failure to provide particular conditions for synchronization and for differentiation. The as-filed specification indicates that in an "exemplary embodiment," the synchronization step is carried out in "steel factor (50ng/ml), Flt-3 (100ng/ml), and thrombopoietin in Teflon bottle cultures," i.e. omitting the concentration of thrombopoietin. The specification also provides no concentrations for the GM-CSF or G-CSF employed in the differentiation step. See page 6, line 26, through page 7, line 2; page 10, lines 16-20; and Figure 1. The most information the specification provides about GM-CSF and G-CSF is that they were "used together at three different log-dilutions," but this fact is both confusing and inadequate to disclose the amounts. Given the specification's limited nature, the skilled artisan would need to

carry out trial-and-error experiments to determine the concentrations of GM-CSF and G-CSF that give the required outcomes. If applicant's statement that the effects of these factors are unpredictable is correct, that statement could be construed as an admission that the specification is not enabling for the claimed method. The examiner declines to treat the statements as such in this Office action, but persistent urgings along these lines will be interpreted as an admission that identifying the proper conditions for the claimed method would have required more than routine experimentation at the time of the invention.

Claims 66, 67, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara, Yan, and Messner as applied to claims 1-4, 6, 11, 13, 29, 30, 65, 68-72, and 74-81 above, and further in view of McGlave et al. (1997, U.S. Patent 5,605,829; reference A).

Hagihara, Yan, and Messner are relied upon as above. These references do not teach isolating BMSCs by fluorescence activated cell sorting (FACS).

McGlave teaches isolating pluripotent CD34+ BMSCs using FACS. See column 2, lines 8-25.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the FACS isolation step of McGlave for the density centrifugation step of Hagihara because McGlave teaches that FACS isolates a pure population of CD34+ cells. The skilled artisan would have been motivated to make the substitution because Hagihara recognized CD34+ cells as the important ones obtained in their

density gradient centrifugation step, so the skilled artisan would have wanted to conduct Hagihara's method with as pure a population of useful starting material cells as possible.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Applicant's comments have been fully considered, but they are not persuasive of error because they do not particularly address these claims other than to note their addition to the application. See page 17.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651